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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
KOLKER, DANIEL E

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 07/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/036,342	GODDARD ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-30 and 32 - 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-30 and 32-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/17/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5-02

DETAILED ACTION

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.Applicant's remarks, amendments, and declarations filed 17 June 2005 have been entered in full. Claim 31 has been cancelled, no new claims have been added.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

4. The information disclosure statement filed 17 June 2005 has been considered. The BLAST results indicate that applicants are aware of nucleic acids and proteins with identity or homology to the one claimed herein. However the results cannot be considered because there is no alignment provided, nor is there an indication of the percent identity between the claimed sequence and the reference sequences. Applicant states on p. 8 of the remarks that the newly-submitted documents include references to specific accession numbers and sequences. Applicant is advised that the BLAST results submitted appear to be a list of sequences which match, but do not provide either alignments or indications of how the sequences are related to the instantly-claimed peptides. Therefore the examiner cannot determine if the sequence accession numbers submitted by applicant constitute prior art. Furthermore the search results submitted appear to be the results are not publicly available documents. Applicant is directed to MPEP 609 and 37 CFR 1.97 and 1.98.

Withdrawn Objections and Rejections

5. The following objections or rejections made in the previous office action are withdrawn:

The objections to the specification. Applicant has deleted the hyperlinks and changed the title.

The rejections of claims 22 – 30 and 32 – 34 under 35 USC 112 for failing to comply with the enablement requirement, as far as it relates to deposit of biological material. Applicant's declaration filed 17 June 2005 is sufficient to overcome the rejection.

The rejections under 35 USC 112, second paragraph. Applicant has amended the claims to recite specific residues for the extracellular domain and deleted confusing language relating to the extracellular domain without the signal peptide.

The rejections of claims 22 – 27, 29 - 30, 33, and 34 under 35 USC 102. The declaration filed on 17 June under 37 CFR 1.131 is sufficient to overcome the Ruben reference.

Rejections Maintained

Claim Rejections - 35 USC §§ 101 and 112

6. Claims 22 – 30 and 32 – 34 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The rejection is maintained for the reasons made of record in the previous office action and reiterated below.

The claims are drawn to isolated polypeptides, called PRO4380, as well as variants at least 80% identical thereto fragments of same, and chimeric polypeptides. The specification asserts that PRO4380 has two specific utilities, as it came up positive in two assays, however neither utility is substantial.

Applicant did not address the examiner's arguments that the first assay, Example 37 (page 166), drawn to compounds which test positive as either stimulators or inhibitors of glucose or FFA uptake. This assay is deemed to lack utility for the reasons made of record in the previous office action.

The data presented in Example 41 (p. 168 – 169) of the specification indicate that PRO4380 was positive in the Mouse Kidney Mesangial Cell Proliferation Assay. It is acknowledged that proliferation of mammalian kidney mesangial cells is useful. However, the threshold used in determining whether a particular PRO molecule counts as "positive" in this assay would not be considered reasonable by one of skill in the art. The specification discloses (p. 169, lines 1 – 2) that positives in this assay include anything which is at least 15% over the control reading. The post-filing publication by Rovin et al. (2002. Kidney International 61:1293-1302) indicates that a 21% increase in human mesangial cell proliferation is not statistically significant (see particularly p. 1296, lines 3 – 6).

On page 9 of the remarks applicant refers to the utility guidelines on specific, substantial, and credible utilities. The claims were not rejected for lack of a specific or credible utility, thus

arguments related to those (i.e page 9, points (1) and (3) in the final paragraph) are not germane. Particularly, the citation of MPEP 2107 II (B)(1)(ii), drawn to credible utilities is not on point as no rejection for lack of credibility was made.

On p. 10 of the remarks, applicant argues that utility need not be proven, that a reasonable correlation between the evidence and the asserted utility is sufficient, and that the asserted utility should be accepted if it is more likely than not true. Applicant cites *In re Langer*, *In re Jolles*, *In re Irons*, *In re Sichert*, *Raytheon v. Roper*, and *In re Oetiker* as supporting this argument. Applicant's arguments have been fully considered but are not persuasive.

In *In re Langer*, the court ruled the Patent Office cannot require clinical testing in humans to rebut a prima facie case for lack of utility. In the instant case, the Office has not made such a requirement. Furthermore the Langer court ruled that "Assuming that sufficient reason to question the statement of utility and its scope does exist, a rejection for lack of utility under § 101 will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the statement of utility and its scope as found in the specification are true." In the instant case there is in fact sufficient reason to question the statement of utility. The reference by Rovin cited in the previous office action indicates that the 15% threshold used by applicant is not reasonable. Therefore one of skill in the art would have reason to doubt the asserted utility.

In *In re Jolles*, the issue was whether data from an art-recognized animal model could be considered predictive of results in humans. That is not an issue in the instant case, as the examiner indicated in the paragraph spanning pp. 5 – 6 of the previous office action that proliferation of mammalian kidney mesangial cells would be useful. But since the threshold used by applicant was 71% of a change shown not to be statistically significant, one of skill in the art would conclude that there PRO4380 does not induce any more mesangial cells than are induced under control conditions.

The citation of *In re Irons* is also not relevant to the instant case. In *Irons*, evidence was submitted that indicated that the drug had been administered to 888 patients and that statistically significant results were obtained showing an improvement in arthritic conditions. In the instant case, no such evidence has been submitted. In the instant case, the claimed product has not been administered to patients. Furthermore, there is no evidence of record indicating a statistically significant result in vitro.

The *Sichert* court ruled that blind comparative studies of the claimed compositions, which showed that the compositions were effective in relieving lymphatic congestion (as

narrowly defined), were sufficient to establish utility of said compositions under 35 USC § 101. In the instant case, applicant has not shown any such studies, and therefore because the fact pattern is sufficiently different the *Sichert* case is not germane.

In *Raytheon v. Roper*, utility was found by the Federal Circuit when a lack of utility had been found by a lower court. This was due not to the sufficiency of the evidence presented, but rather because the Federal Circuit ruled that the claims in question had been interpreted erroneously. In the instant case, there does not appear to be a question as to how the pending claims are being interpreted.

It is not immediately apparent why applicant has cited *In re Oetiker* in arguments related to the utility under 35 USC § 101, as the *Oetiker* case dealt not with utility but with obviousness under 35 USC § 103. No claims have been rejected under § 103 in the instant case.

The examiner acknowledges that the ability to induce mesangial cell proliferation is specific. However, the assay used by applicant and reported in Example 41 beginning on p. 168 of the specification would not allow a skilled artisan to conclude that it is more likely than not that the asserted utility is true and therefore the asserted utility is not substantial.

On p. 11 of the remarks applicant discusses the examiner's interpretation of the results from Rovin. The examiner and applicant appear to agree on this point. Rovin clearly stated that the data point, a 21% increase, did not represent a significant difference due to the large degree of variability inherent in this assay. Because of the large degree of error, a 21% increase is not significant. Stated another way, one of skill in the art would recognize that it is *improper* to conclude that the two samples (control and 5 uM ciglitazone) are drawn from different populations.

Significance does not mean, as applicant asserts on p. 11 of the remarks, that there is not an overlap of standard deviations or errors in the data set. Rather, statistical significance is a determination, based on mathematic procedures, that the observed difference between samples has a less than 5% chance of occurring by random accident (see attached definition from the On-line Medical Dictionary, accessed 22 July 2005). Applicant argues that Rovin's report of a 21% non-significant difference indicates that the statistical error in their measurement overlaps with the statistical error in the control set, and that "this does not mean that an increase of proliferation of 21% is not scientifically important or significant, but means that Rovin's particular measurement of 21% may be incorrect due to the amount of error for that data point." This is not the way significance is understood in the art. Significance is an inference. When a

result reaches statistical significance, it is proper to infer that the two samples are drawn from separate populations. When the result is not significant, the appropriate inference is not that the particular value is subject to error, but rather that it is not possible to tell if the two samples were drawn from separate populations. Applicant is directed to the attached text from the chapter by Freund et al. (2003. Statistical Methods, Second Edition, pp. 117 – 138), particularly the definition of "significance level" on p. 126 and the definition of "p value" on p. 133 for a more complete understanding of the way statistics are used in scientific papers. In the instant case, Rovin et al. used analyses of variance, followed by post-hoc Bonferroni-corrected pairwise comparisons (see p. 1295, second column "Statistical Analysis") rather than the standard argued by applicant. The teachings of Rovin indicate that this assay has so much variability that even if a 21% difference is detected when 12 experimental and 12 control samples are provided (see legend for Figure 2 which indicates that "[e]ach point represents the mean of at least 3 individual experiments done in quadruplicate".

On p. 12 of the remarks, applicant points out that Rovin found an 18% increase was significant. Applicant again asserts his own definition of significance (p. 12, second paragraph) which contradicts that provided on p. 1295 of Rovin. It is noted that this level is still greater than the changes reported in the specification, where only a 15% increase is considered important. However, taken with the finding that a 21% increase in this assay is not significant, this finding further supports the examiner's point that knowing the variability associated with the measurements is crucial to determining whether or not the artisan will conclude that samples are drawn from different populations. In the instant case, the specification does not disclose the variability in the sample, so a skilled artisan would not reasonably conclude that PRO4380 induces mesangial cell proliferation. Thus the rejection under 35 USC § 101 stands.

7. Claims 22 – 30 and 32 – 34 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

8. Even if enablement were found for PRO4380, enablement would not be commensurate in scope with claims 22 – 30 and 32 - 34, because the specification does not reasonably provide enablement for polypeptides 80%, 85%, 90%, 95%, or 99% identical to SEQ ID NO:57 which have the ability to induce mesangial cell proliferation. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant is directed to paragraph number 6 for a more complete discussion of why claims to SEQ ID NO:57 are not deemed to be able to induce mesangial cell proliferation. In summary, applicant has shown that in a single trial, SEQ ID NO:57 induced a 15% increase in the number of mesangial cells. Applicant did not disclose the variability in this system, and Rovin teaches that the variability in this assay is so high that even a 21% change, calculated as the difference between the average of 12 experimental and 12 control samples, is not significant. Freund teaches that it is not proper to conclude that samples are drawn from separate populations when the test statistic exceeds the significance level. In the instant case, the assay performed by Rovin appears to be identical to that performed by applicant. Both used mammalian mesangial kidney cells, and even used the same detection reagent from Promega. The teachings of Rovin indicate that knowing the variability level of the assay is crucial to making conclusions as to whether or not the differences are significant. Because applicant's results fall below both the lowest level shown by Rovin to be significant, and below a level shown by Rovin to be non-significant, a skilled artisan would not conclude that SEQ ID NO:57 increases mesangial cell proliferation. Instead the artisan would conclude that the ability of SEQ ID NO:57 to induce proliferation is no different than that of a control.

On p. 13, second complete paragraph of the remarks applicant refers to pp. 109 – 111 of the specification as providing guidance as to how to make the claimed variants. However this text does not indicate which regions of PRO4380 (i.e. SEQ ID NO:57) are to be retained and which regions can be altered. Thus an artisan would have to resort to undue experimentation in order to make and use the claimed variants, as there is not sufficient guidance in the specification.

9. Claims 22 – 26 and 33 – 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicant argues that the legal standard for the written description requirement is whether the disclosure "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." The examiner agrees with applicant's definition.

Applicant argues that the amendments to the claims, particularly the recitation "has the ability to induce mesangial cell proliferation" is sufficient to overcome the written description rejection. The examiner disagrees. The specification does not disclose any polypeptide sequences at least 80, 85, 90, 95, or 99% identical to SEQ ID NO:57 which have the stated activity, with the sole exception of SEQ ID NO:57 itself. The claims are drawn to genera of polypeptides, but only a single member of the genus is disclosed. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a polypeptide, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606." While the preceding quotation is drawn to DNA, the same logic applies to claims drawn to proteins and their variants.

Furthermore applicant has not shown which regions of the protein are important for the claimed activity. A description of a genus of proteins may be achieved by means of a recitation of a representative number of proteins, defined by amino acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polypeptide sequence SEQ ID NO:57. The additional limitation of requiring that

the protein variants have the ability to induce mesangial cell proliferation fails to meet the written description requirement and thus claims 22 – 26 and 33 – 34 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 112

10. Claims 22 – 30 and 32 – 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims have been amended to recite "wherein the extracellular domain is amino acids 293 – 507". There is no disclosure of this region being the extracellular domain. Figure 26 of the specification indicates the location of a transmembrane domain, but there is no disclosure of which end of the protein is intracellular and which end is extracellular. Since there was not disclosure of which regions were intracellular or extraceullar in the specification, drawings, or claims as originally filed, identification of such regions is deemed to be new matter.

New Rejections and Objections

Oath/Declaration

11. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration, particularly the changes to citizenship by Zhang and to address by Eaton. See 37 CFR 1.52(c).

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent

> granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 22 – 27, 29 – 30, and 33 - 34 rejected under 35 U.S.C. 102(e) as anticipated by (U.S. Patent application publication 2003/0100051, published 29 May 2003, filed 10 September 2001, claiming priority to applications filed 28 June 2001, 10 November 1999, 6 May 1999, and claiming benefit of provisional applications filed 11 September 2000, 18 May 1998, and 12 May 1998).

Ruben et al. teach SEQ ID NOs:137, 139, and 242, each of which are 97.0% identical to applicant's SEQ ID NO:57 (see attached alignments). Ruben's sequences are identical to applicant's SEQ ID NO:57 from residues 16 – 507 (using applicant's residue numbers). Applicant has identified residues 1 – 26 as the signal peptide (see Figure 26). Since the sequences from Ruben et al. are 100% identical to SEQ ID NO:57 starting at residue 16, the prior art sequence also meets the limitations of claims 27, 29, and 31, drawn to polypeptides comprising SEQ ID NO:57 lacking its associated signal sequence, independent of which end of the polypeptide is the extracellular domain. Similarly, the teachings of Ruben also anticipate claims 27 and 30, which are drawn polypeptides comprising the extracellular domain of SEQ ID NO:57. As mentioned in the previous office action, signal sequences are cleaved from proteins as they are processed. Therefore, the sequence from Ruben et al. comprises the extracellular domain of SEQ ID NO:57, as the two are 100% identical with the exception of the signal sequence. Ruben also teaches fusion polypeptides comprising the claimed proteins and epitope tags, including the Fc domain of immunoglobulin (see p. 114, paragraph 0773 of Ruben), meeting the limitations of claims 33 – 34. The claims, as amended, recite the functional limitation requiring that the polypeptide has the ability to induce mesangial cell proliferation.; Ruben is silent as to this property. However, since the only differences between the prior art product and applicant's product is in the signal sequence which is cleaved off during protein processing, Ruben's polypeptides will inherently have the claimed properties.

It is acknowledged that applicant's declaration under 37 CFR 1.131 is sufficient to indicate that he was in possession of the claimed material prior to 18 November 1999. However the publication by Ruben cited herein claims benefit of provisional applications filed 12 May 1998 and 18 May 1998. These are the same applications cited on the face of WO 99/58660, which was the basis of the rejection under 35 USC 102 (a) in the previous office action.

Conclusion

14. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.
July 27, 2005

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER